

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Johannes REINMUELLER, et al. : Group Art Unit.: 1623

Serial No.: 10/586,345 : Examiner: Scarlett Y. Goon

Filed: July 13, 2006 :

Title: COMPOSITION FOR TREATING INFLAMMATORY DISEASES

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

I, Dr. Johannes Reinmüller, being duly warned, declare that:

I am a co-inventor of the present application, and I am familiar with the prosecution thereof, including with the Office Action issued on October 23, 2009, with the references cited therein, and with the Response filed on March 23, 2010.

My CV is attached demonstrating my qualification to make this declaration.

Hyaluronic acid is a naturally occurring compound, which is present in the connective tissue and in body fluids, wherein the hyaluronic acid is always bound to proteins, so-called hyaluronic acid binding proteins. The technical production and purification of hyaluronic acid thus results in the production of an artificial product, namely uncrosslinked hyaluronic acid. In an aqueous solution, the unbranched long-chain macromolecules of uncrosslinked hyaluronic acid are present in a so-called random coil formation, in which form the product is used for medical purposes.

When being administered, e.g., intradermally by means of an injection needle, uncrosslinked hyaluronic acid is able to distribute extensively, i.e., not only punctually, within the dermis, with a large concentric area being infiltrated by means of a single injection point. Thus,

administration of uncrosslinked hyaluronic acid to several distinct areas allows an extensive, i.e., not only punctual, treatment of, e.g., inflammatory skin diseases.

By crosslinkage, water-insoluble gels or precipitates having a high viscosity are produced from soluble, uncrosslinked hyaluronic acid. Depending on the precipitation process, the viscoelastic properties of crosslinked hyaluronic acids may widely vary. In general, however, crosslinked hyaluronic acids are very elastic. Consequently, crosslinked hyaluronic acids can hardly be injected via small needles into the skin and are applied topically instead, as evidenced by Sakurai (US 4,716,224). In order to allow for an intradermal administration, conventional crosslinked hyaluronic acids must be modified.

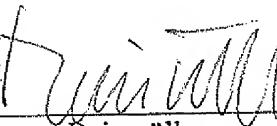
In order to be injectable into the skin at all, crosslinked hyaluronic acids must be shred to small particles having a size of between 250 and 750 micrometers at the most. However, particles of crosslinked hyaluronic acid having a size of between 250 and 750 micrometers are not able to distribute within the tissue, as it is the case with uncrosslinked hyaluronic acid due to these particles forming clusters and lifting the surface of the injection sites. This lifting effect can be desired in cosmetic treatments indeed.

The viscoelastic properties of crosslinked hyaluronic acids and the accumulation of small particles thereof in clusters would have motivated one of ordinary skill in the art away from intradermally administering the compound in diseases requiring an extensive, i.e., not only punctual, treatment. In order to be useful in the treatment of inflammatory skin or mucous membrane diseases, the viscoelasticity and/or the particle size of conventional crosslinked hyaluronic acids must be further reduced, such that the particles are able to extensively spread within the tissue following administration.

In sum, one of ordinary skill in the art would not have considered intradermally administering the crosslinked hyaluronic acid of Sakurai in the method of Petrigni or Falk due to the above-discussed properties or behaviour of crosslinked hyaluronic acid. Hence, one of ordinary skill in the art would not and could not have arrived at the subject matter of the present application based on a combination of Petrigni and Sakurai, or, in the alternative, based on a combination of Falk, Sakurai and Fischer.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 21th, 2010
Date



Dr. Johannes Reimüller

Dr. med. Johannes Reinmüller

A Short Biography

Klinik am Sonnenberg, Leibnizstraße 19, 65191 Wiesbaden, Germany

Dr. Reinmüller is Chief Physician, and Plastic Surgeon, at the private Klinik am Sonnenberg in the spa town of Wiesbaden in Germany. In the early 1990s, he collaborated with Biomatrix and pioneered the use of hyaluronic acid (HA) for soft tissue augmentation, with the design and development of Hylaform®. He then became involved with the development of Restylane®, and was principal investigator for the product in Q-Med's first clinical trial. Subsequently, Dr. Reinmüller was the principal investigator for a clinical study examining the performance and safety of Mentor's double crosslinked HA dermal filler, Puragen™. Furthermore he was the principal investigator in the Belotero™ multicenter study of Merz Pharmaceuticals in 2005.

He is an author of a recently published text book of Cambridge University Press "Office-Based Cosmetic Procedures and Techniques" edited by Sorin Eremia and of numerous scientific publications.

Dr. Reinmüller has a keen scientific interest in soft tissue fillers, both synthetic and natural, sparked by his work with Professor Gottfried Lemperle (inventor of Artecoll) in the 1980s. Since then, Dr. Reinmüller has played an active and significant role in the innovative use of a variety of implant materials for a spectrum of aesthetic indications. For example, he has patented a novel method for crosslinked HA, and other biomaterials, in the treatment of hypertrophic (keloid) scars.

Moreover, Dr. Reinmüller is an expert of surface modifications of medical implants and the inventor of several biological coatings and new medical devices including drug release systems, suction drainage tubes and anticoagulant and antibacterial catheters.

Over the past ten years, Dr. Reinmüller has shared his unique expertise, by training physicians in cosmetic facial augmentation techniques at workshops across Germany and Great Britain. More recently, he has made presentations on dermal fillers at prestigious meetings of the American Society for Aesthetic Plastic Surgery in Vancouver, the International Society for Dermatologic Surgery in Dublin, the International Master Course on Aging Skin in Paris, of the Dermatologic Society of Japan in Kyoto, at the Facial Aesthetic Conference and Exhibition in London, of the European Academy of Dermatology and Venereology in Vienna and at the 21st World Congress of Dermatology in Buenos Aires.

Since 1988: Klinik am Sonnenberg GmbH, Wiesbaden
Clinic Director and Plastic Surgeon.

1986 – 1988: **Frankfurt am Main**
Qualified as specialist in plastic surgery (Professor G. Lemperle).

1982 – 1986: **Wiesbaden & Ulm**
Trained in accident and orthopedic surgery, including one year of research in experimental accident surgery at the University of Ulm (Professor C. Burri).

1975 – 1981: **Frankfurt & Bad Kreuznach**
Surgical training. Qualified as general surgeon.

1977: **University of Mainz**
Promotion. Thesis: "Über die Wechselwirkung von Desoxyribonukleinsäuren mit Proteinoberflächenfilmen an der Luft-Wasser-Grenzfläche" (On the Interaction of Desoxyribonucleic Acid and Protein Surface-Films at the Air-Water Interface)

1975:
Practiced as medical intern and qualified as physician.

1972 – 1975: **Physiologisch-Chemischen Institut, University of Mainz**

Research position studying physiological chemistry. Scholarship at National Laboratory, Oakridge, Tennessee (Oscar Miller jr.) and at New York Medical School (A.K. Kleinschmidt).

1966 – 1971: **University of Mainz**
Obtained medical degree.

1947:
Born in Frankfurt am Main, Germany. Austrian Citizenship succeeding the father's.